Clinical Impact of Viability guided Angioplasty after Acute Myocardial Infarction

van Loon, R.B.

2015

document version
Publisher's PDF, also known as Version of record

5.

LONG-TERM FOLLOW-UP OF THE VIABILITY GUIDED ANGIOPLASTY AFTER ACUTE MYOCARDIAL INFARCTION (VIAMI) TRIAL

Ramon B. van Loon, Gerrit Veen, Stefan J. Schuurmann, Leo H.B. Baur, Otto Kamp, Jean G.F. Bronzwaer, Jos W.R. Twisk, Freek W.A. Verheugt, Albert C. van Rossum

International Journal of Cardiology 2015, 186: 111-116

ABSTRACT

Background: Patients with ST-elevation myocardial infarction (STEMI) not treated with primary or rescue percutaneous coronary intervention (PCI) are at risk for recurrent ischemia. In non-high risk patients, with proven viability in the infarct-area, the VIAMI trial showed benefit of early in-hospital stenting of the infarct-related coronary artery for the composite of death, myocardial infarction (MI), or unstable angina (UA) at 1 year follow-up. In this study we evaluated the long-term outcome (median 8 years) of patients included in the VIAMI-trial.

Methods: After being stable during the first 48 hours of their acute MI, we randomly assigned 216 patients with viability to an invasive (PCI) or a conservative (ischemia-guided) strategy. The primary outcome was the composite endpoint death any cause, recurrent myocardial infarction, or unstable angina. The secondary outcome of this study was the need for (repeat) revascularization.

Results: The combined endpoint of death, recurrent MI and UA was 20.8% in the invasive group and 32.7% in the conservative group (Hazard ratio 0.59; 95% CI 0.36-0.99, p=0.049). No differences were seen in death (8.5% vs. 8.2%, p=0.80) or MI (7.5% vs. 10.9%, p=0.48). Only UA showed a significant difference (4.7% vs. 13.6%, p=0.002). Repeated revascularization was performed in 22.6% of the invasive group and 41.8% of the conservative group (Hazard ratio 0.43; 95% CI 0.29-0.74, p<0.001).

Conclusion: In patients with acute MI (treated with thrombolysis or without reperfusion therapy) and proven viability in the infarct-area, we demonstrated a long-term benefit of early in-hospital stenting of the infarct-related coronary artery.

BACKGROUND

In patients with ST elevated myocardial infarction (STEMI) the newest AHA/ACC and ESC guidelines recommend an early pharmacoinvasive strategy after thrombolysis in all patients (<24 hours). These recommendations are supported by many randomized clinical trials and two meta-analyses [1,2]. In the previous AHA/ACC guidelines angiography should be considered, especially in non-high risk patients (class IIb, LOE C)[3].
In this non-high risk patients group with proven viability in the infarct-area, the VIAMI-trial showed benefit of early in-hospital stenting of the infarct-related coronary artery for the composite of death, MI, or unstable angina at 1 year follow-up (Trial registration: NCT00149591)[4].
We present the long-term follow-up of composite primary endpoint (death, myocardial infarction (MI) and unstable angina (UA)) of the VIAMI trial.

METHODS

Study design

The design of the VIAMI trial has been published previously [5]. In short, the VIAMI-trial was a prospective, multicenter, randomized, controlled clinical trial (RCT). Between April 2001 and January 2006, 291 patients were enrolled from 11 participating Dutch hospitals.

Patients

Patients between 18 to 80 years of age were included in the study when they had a definite myocardial infarction, as demonstrated by an significant rise in creatine kinase-MB levels (twice the upper limit of normal: ULN), 1 mm ST segment elevation in two or more standard leads or 2 mm ST segment elevation in two contiguous chest leads, and/or the development of Q waves.
Patients admitted to the hospital within 6 hours of symptom onset, received thrombolysis combined with heparin. Patients admitted more than 6 hours after symptom onset were considered too late for intervention and therefore only treated with heparin or low weight molecular heparin (LWMH).
The criteria for exclusion were: viability testing technically impossible (poor echo-window), contraindications for dobutamine echocardiography (arrhythmia), and/or coronary angiography (severe diabetic nephropathy or known contrast-allergy), serious life-threatening non-cardiac illness, ECG abnormalities making the evaluation of the ST segment impossible (left bundle branch block, pacemaker), and an unreliable follow-up.
The collection of long-term follow-up was planned in the protocol and approved by the authorized ethics committee. All patients provided written informed consent.

Randomization and study protocol

Patients who remained stable and revealed no signs of ongoing ischemia, underwent low dose dobutamine echocardiography (LDDE) for the detection of viability within 72 hours after AMI. Dobutamine is administrated intravenously at doses of 5, 10, and 15 μg/kg/min, for 5 minutes at each dose. When a 10% increase in heart rate is not achieved with 15 μg/kg/min, a 5-minute infusion with 20 μg/kg/min can be used as the final stage of the procedure. This test was performed according to the guidelines of the American Society of Echocardiography [6]. Viability was defined as the improvement of wall motion abnormalities (WMA's) in two or more segments of the infarct zone. Patients without WMA's were not included in this trial. In case of poor acoustic window ultrasound contrast agents were used to improve image quality and diagnostic yield. All images were sent to the core-lab (VU University Medical Center, Amsterdam, The Netherlands) and were analyzed by 2 experienced observers. A third observer was used in case of disagreement to reach consensus. Patients with an ischemic response in at least 2 segments were excluded from the study because coronary angiography was mandatory.
Patients with viability in the infarct-area were randomized to an invasive or a conservative treatment strategy. All patients were treated according to international guidelines with aspirin, beta blockers, angiotensin-converting-enzyme inhibitors, and statins. Patients randomized to the invasive strategy underwent in-hospital coronary angiography with the intention to perform PCI with stenting of the infarct-related coronary artery (IRA) and concomitant use of abciximab. Angiography and PCI was performed as soon as possible after randomization. Patients randomized to the conservative strategy received an ischemia-guided approach with stress testing before hospital discharge. Coronary angiography was recommended in case of a positive test for ischemia. If an ischemia-guided intervention was performed before discharge, it was considered planned and not interpreted as an event. Patients without viability served as a registry group also with a long-term follow-up.

Follow-up

Patients were contacted by telephone more than 5 years after randomization (mean 8 years). All potential cardiac outcome events were recorded; hospitalizations were reviewed for potential cardiac outcome events. If a patient could not be contacted, information was obtained from the patient's family, general practitioner, treating cardiologist, and hospital records. Follow-up was censored at the date of last telephone contact or, if patient was lost to follow-up, at the date of last clinical follow-up.

Clinical outcomes

The primary outcome was the composite endpoint death any cause, recurrent myocardial infarction, or unstable angina. The secondary outcome of this study

was the need for (repeat) revascularization. A recurrent myocardial infarction was defined as a history of chest discomfort and ECG changes indicative for trans mural ischemia or necrosis, with an 2 times ULN increase in the total creatine kinase and MB isoenzyme activity. Reinfarction during initial hospitalization required a decrease of cardiac enzymes, followed by a subsequent rise to a level of 2 times ULN and 50% above a previous measured value.
Unstable angina was diagnosed in patients who were rehospitalized with ischemic chest discomfort at rest or with minimal exertion, and with the need for intravenous medical intervention and/or objective evidence of myocardial ischemia.

Statistical analysis

The VIAMI-trial was conducted to investigate the differences in clinical outcome between an invasive and a conservative strategy in patients with demonstrated viability in the infarct-area.
Baseline descriptive data are presented as a mean ± standard deviations (SD). Differences in clinical and echocardiographic variables are assessed by unpaired Student's t-test. Differences between proportions are assessed by chi-square analysis; a Fisher's exact test is used when appropriate. Event-free survival curves are computed with the Kaplan-Meier method. The treatment groups were compared with log-rank
tests without adjustments for covariates. Hazard ratios with 95% confidence intervals (CI) were obtained with Cox proportional hazards models, with treatment allocation as the only covariate.
All analyses were performed on an intention-to-treat basis. All analyses were performed with the use of SPSS software, version 16.0 (SPSS, Inc., Chigago, Illinois).

RESULTS

Baseline characteristics

In total 291 patients were enrolled in the VIAMI-trial. The viable patients were randomized to an invasive strategy (106 patients) or to a conservative strategy (110 patients). A total of 75 non-viable patients served as a registry group. During the long-term follow-up, no information was collected in 14 patients. These patients were considered lost to follow-up (4.8%) (Figure 1).
The characteristics of the patients at admission and discharge are depicted in Table 1. Except for a lower prevalence of statin use in the group assigned to the conservative strategy (p=0.02), no significant differences are present. The treatment of the index infarction in both groups was well comparable with 53% of patients receiving thrombolysis in the invasive group and 45% in the conservative group. The time from onset of symptoms to the start of fibrinolytic therapy was also comparable in both groups.
Cardiac catheterization was performed in 99% of patients in the invasive strategy group (1 patient died before the assigned catheterization) resulting in a percutaneous

intervention (PCI) in 73% of these patients. Coronary-artery bypass surgery was performed in 11% because of high risk anatomy. Eventually, 16% did not receive a revascularization procedure at all, mainly due to non-significant coronary artery disease or a small culprit vessel not suitable for PCI. Medical therapy at discharge was almost similar in both randomized groups, except for the use of clopidogrel, which drug was obligatory in patients with a stent. There was also a significant higher use of calcium inhibitors in the conservative treated patients (14% vs. 4%, p=0.02).

Trial profile

Figure 1

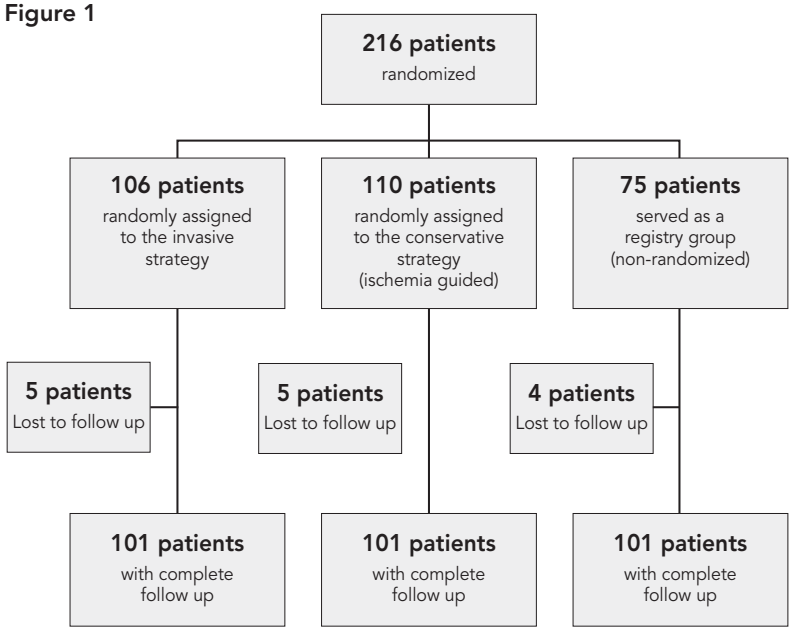


Table 1: Baseline characteristics of the patients

Characteristic	Viable		Non-viable	p- value*
	Invasive (n = 106)	Conservative (n = 110)	(n = 75)	
Male	75%	81%	66%	0.41
Age (years)	60	59	64	0.52
Clinical history (%)				
Angina	41%	44%	54%	0.68
Myocardial infarction	6%	4%	9%	0.53
Percutaneous coronary intervention	2%	3%	9%	1.0
Coronary-artery bypass grafting	0%	1%	1%	1.0
Risk Factors (%)				
Dabetes mellitus	8%	13%	12%	0.26
Hypertension	27%	28%	30%	1.0
Hypercholesterolemia	19%	14%	18%	0.36
Current cigarette smoking	45%	40%	64%	0.49
Family history of CAD	33%	31%	20%	0.77
Medications at admision (%)				
Aspirin	17%	9%	14%	0.11
Beta-blocker	12%	12%	18%	1.0
Ca-inhibitor	9%	4%	8%	0.16
Statins	15%	6%	12%	0.02
ACE-inhibitor	8%	6%	15%	0.59
AT II antagonist	6%	6%	5%	1.0
Medication at discharge (%)				
Aspirin	95%	99%	88%	0.21
Beta-blocker	97%	93%	92%	0.33
Ca-inhibitor	4%	14%	8%	0.02
Statins	94%	99%	92%	0.12
ACE-inhibitor	54%	58%	68%	0.67
AT II antagonist	3%	7%	8%	0.33
Clopidogrel	71%	21%	28%	<0.001
Time from onset of symptoms	73±32	69±25	78±31	0.53
To randomization - hr				
Time from onset of symptoms	184±155	200±147	190±112	0.65
To thrombolysis - minutes				
Trombolysis	54%	45%	47%	0.34
Anterior infarction	31%	33%	47%	0.88
Ejection Fraction (EF%)	52.7%	54.7%	53.5%	0.32
Randomization				
Protocol PCI (%)	73			
CABG (%)	11			
No revascularization (%)	16			

** Differences between the randomized groups are expressed with a P-value. Plus-minus values are means ± SD.*

Primary and secondary endpoints

The primary endpoint occurred in 58 patients (22 patients (20.8%) in the invasive group and in 36 patients (32.7%) in the conservative group. By intention-to-treat analysis the long-term event-free survival was 78% percent in the invasive strategy group and 66% in the conservative strategy group (Hazard ratio, 0.60; 95 percent confidence interval, 0.36 to 0.99; p=0.049)(Figure 1 and Table 2). Mortality after long-term follow-up was 8.5% in the invasive group vs. 8.2% in the conservative group (p=0.80). Myocardial infarction occurred in 7.5% in the invasive group vs. 10.9% in conservative group; p=0.48). There is a significant difference in the occurrence of UA between the two randomized groups (4.7% vs. 13.6%; p=0.002) in favor of the invasive strategy.

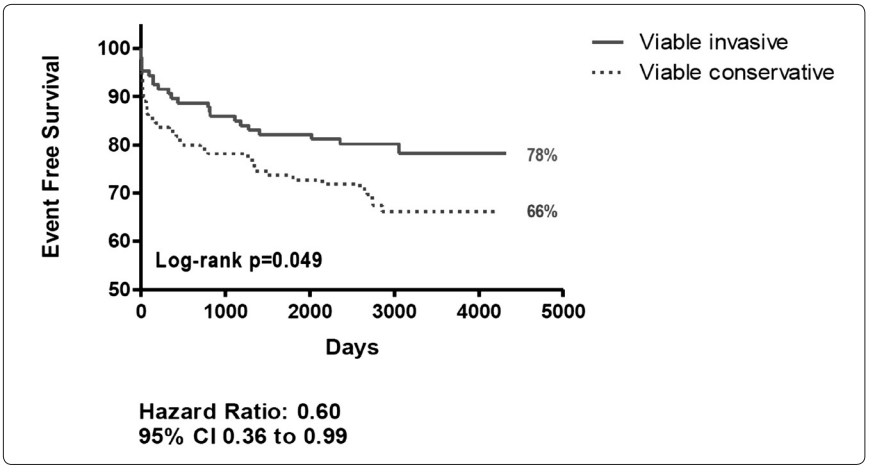
The secondary endpoint occurred in 70 patients. In the invasive group 24 patients (22.6%) underwent a (repeat) revascularization vs. 46 patients (41.8%) in the conservative group (Hazard ratio 0.43; 95% CI 0.29-0.74, p<0.001)(Figure 3).

Table 2: Components of primary end points

	Invasive (n = 106)	Conservative (n = 110)	p- value*
Composite	22 (20.8%)	36 (32.7%)	0.047
Mortality	9 (8.5%)	9 (8.2%)	0.80
Acute MI	8 (7.5%)	12 (10.9%)	0.48
Unstable Angina	5 (4.7%)	15 (13.6%)	0.002

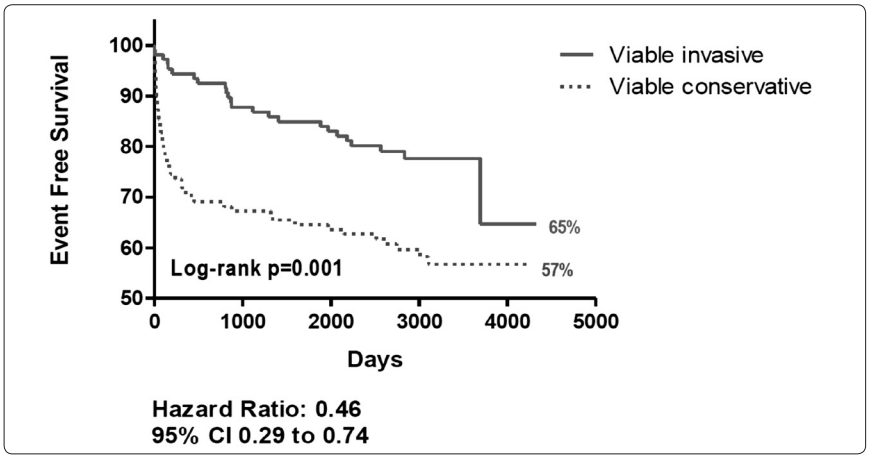
** P-values calculated with Fisher-exact test.*

Figure 2



Kaplan-Meier estimates of the cumulative rate of;
The composite primary end point of death from any cause, recurrent infarction and unstable angina. Viable invasive vs. viable conservative strategy.

Figure 3

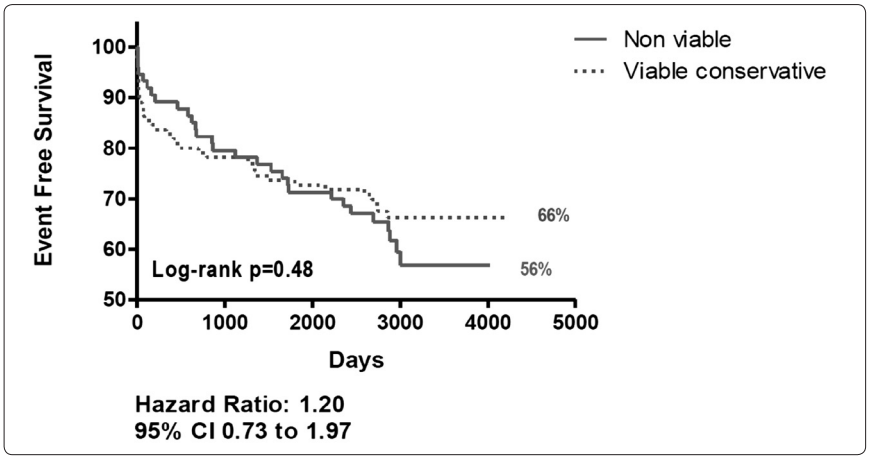


Kaplan-Meier estimates of the cumulative rate of;
The need for repeat revascularization procedures after discharge.
Viable invasive vs. viable conservative strategy.

Outcome in the non-viable group

The non-viable patients are a non-randomized registry group. Nevertheless, they received the same ischemia-guided approach as the viable-conservative patients, making it interesting to compare these two patient groups.
Comparing the viable-conservative and the non-viable group, no significant difference was found in the primary composite endpoint (32.7% vs. 38.6%, p=0.44). Compared to the conservative group, the non-randomized non-viable group showed a trend to an increased mortality (16.0% vs. 8.2%, p=0.16) without any differences in recurrent ischemic events (22.7% vs. 24.5%, p=0.86)(Table 3 and Figure 4).

Figure 4



Kaplan-Meier estimates of the cumulative rate of;
The composite primary end point of death from any cause, recurrent infarction and unstable angina. Non-viable patients (registry) vs. viable conservative patients (randomized).

DISCUSSION

The long-term follow-up of the VIAMI-trial showed a sustained clinical benefit of early in-hospital stenting of the infarct-related coronary artery in patients with proven viability after an acute MI, who were initially treated with thrombolysis or without any reperfusion therapy. We already showed benefit of early in-hospital stenting at 1 year follow-up.
To the best of our knowledge this is the first and only long-term follow up of a RCT comparing early invasive (beyond the time window of expected myocardial salvage) with conservative treatment in patients with a myocardial infarction who were initially not treated with primary PCI.
Analyzing the Kaplan Meier curves, the differences in event free survival mainly arise in de first months after the acute MI. It is known that after successful thrombolysis, more than 50% of patients have a significant residual stenosis and about 20-30% suffer from recurrent ischemic events because of plaque-instability in the infarct-related coronary artery, especially in the first 6 months [7]. This phenomenon applies mainly to the viable but conservative group, because in this group the infarct related artery is still untreated (no PCI) and therefore prone to plaque-instability and re-occlusion. After one year of follow-up, the Kaplan Meier curves run more parallel. The explanation for this observation remains speculative. First; a significant part of the conservatively treated group is also revascularized because of recurrent ischemic complains (31.8%) in the first year of follow up [4]. Second; after one year of follow up cardiac events will also occur in the non-infarct related, non-treated vessels. Therefore, the two groups will more resemble each other with consequently comparable occurrence of cardiac events.
This phenomenon was also seen in the long-term follow up of the NSTEMI trials FRISC II and ICTUS [8,9].

Culprit-vessel vs. non-culprit vessel treatment

In our study we performed a viability guided intervention early (48 to 72 hours) after an AMI in a relatively low-risk population, with the intention to perform only culprit vessel angioplasty. With this approach we achieved a long-term benefit. In the light of the recent publication of the PRAMI-study it could be argued that performing PCI of non-culprit lesions would improve outcome even further.
The Preventive Angioplasty in Acute Myocardial Infarction (PRAMI) trial evaluated a strategy of preventive PCI (multivessel revascularization performed at the time of primary PCI on all vessels with angiographic stenosis ≥50%) against culprit vessel-only strategy in patients with STEMI (n=465) undergoing primary PCI [10]. This trial was stopped prematurely because of a significant reduction in the primary outcome (composite of cardiac death, nonfatal MI, or refractory angina) in the preventive PCI group at a mean follow-up of 23 months (9% versus 21%; P<0.001). In the PRAMI study the composite of reinfarction and refractory angina in the culprit vessel PCI only group was 21.6% which is higher than the composite of reinfarction and refractory angina in the culprit-vessel PCI-arm of the VIAMI-study (12.2%). This difference could be explained by the filtering out of patients

with early signs of recurrent ischemia in the VIAMI study, creating a lower baseline risk at the time of inclusion. Nevertheless, the outcome of both studies support the concept that many patients presenting with an acute myocardial infarction have one or more unstable plaques jeopardizing viable myocardium [11], and that (multivessel) PCI will address these unstable plaques thereby reducing the risk of recurrent ischemia.
For possible confirmation of the PRAMI results we have to wait for the ongoing Complete versus Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE) trial (NCT01740479). This trial will assess whether, on a background of optimal medical therapy with aspirin and ticagrelor, a strategy of complete revascularization involving staged PCI (<72 hours after AMI) using drug-eluting stents of all suitable non–infarct-related artery lesions (visual >70%, or visual >50% with FFR ≤0.80) is superior to a strategy of culprit vessel–only PCI in reducing the primary outcome (composite of cardiac death, nonfatal MI) in patients with multivessel disease who have undergone successful culprit lesion primary PCI for STEMI (n=3900).

Current guidelines

The newest AHA/ACC and ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation recommend an early pharmacoinvasive strategy after thrombolysis in all patients (<24 hours)(class 1 LOE A indication) with a class 2b LOE B indications for immediate revascularization of significant non-culprit lesions during the same procedure as primary PCI of the culprit vessel [1,2,12].
These long-term results of the VIAMI-trial underline this recommendations, at least in part, even in a relatively low-risk population.

Limitations

The definition of AMI has been changed sufficiently during the long-term follow up of the VIAMI-trial [13]. Cardiac troponins were not available in all participating centers. Therefore, we used the older definition for the diagnosis of AMI [14]. Consequently, part of the UA patients would have been scored as a NSTEMI with the new definition resulting in another distribution of our composite primary endpoint. This is probably one of the explanations for having only 7.5% and 10.9% acute myocardial infarctions in our patient groups. Another explanation is the relatively low-risk population.
Furthermore, no standard angiography was performed in the medical treated patient group. As a consequence, no information about the patency of the IRA is available in this patient group, making it impossible to correlate initial infarct location to recurrent infarction location.
The inclusion of the VIAMI-trial took place between 2001 and 2006. Therefore, part of the medical treatment does not apply to today's standard. During the inclusion-period clopidogrel was not standard care in patients without stents.

The use of ACE inhibitors and AT II antagonists is also low at discharge. Especially during the early days of the inclusion, these drugs were only given to patients with anterior infarction and/or left ventricular systolic dysfunction with clinical signs of heart failure [15-17]. Our study population is a low risk patient group with predominantly a preserved left ventricular function. This is, at least in part, a plausible explanation for the low use of ACE inhibitors and ATII antagonists. Consequently, optimal medical treatment according to current clinical guidelines could have been of influence to our results. It is well known that the addition of clopidogrel to aspirin decreases the occurrence of recurrent myocardial infarction in patients treated with fibrinolysis for AMI [18]. Our results would have been less pronounced with standard clopidogrel in all treatment groups.

CONCLUSION

In non-high risk patients with acute myocardial infarction (treated with thrombolysis or without reperfusion therapy) and proven viability in the infarct-area, the first year clinical benefit of in-hospital stenting of the infarct-related coronary artery is sustained during long-term follow-up (median 8 years).

References

1. O'Gara PT, Kushner FG, Ascheim DD *et al*. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: **A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.** *J Am Coll Cardiol* 2013; **61(4):**e78-e140.
2. Steg PG, James SK, Atar D *et al*. **ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation.** *Eur Heart J* 2012; **33(20):**2569-619.
3. Kushner FG, Hand M, Smith SC, Jr. *et al*. 2009 focused updates: **ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update) a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.** *J Am Coll Cardiol* 2009; **54(23):**2205-41.
4. van Loon RB, Veen G, Baur LH *et al*. Improved clinical outcome after invasive management of patients with recent myocardial infarction and proven myocardial viability: **primary results of a randomized controlled trial (VIAMI-trial).** *Trials* 2012; **13(1):**1.
5. van Loon RB, Veen G, Kamp O, Bronzwaer JGF, Visser CA, Visser FC. Early and long-term outcome of elective stenting of the infarct-related artery in patients with viability in the infarct-area: **Rationale and design of the Viability-guided Angioplasty after acute Myocardial Infarction-trial (The VIAMI-trial).** *Current Controlled Trials in Cardiovascular Medicine* 2004; **5**.
6. Schiller NB, Shah PM, Crawford M *et al*. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. **American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms.** *J Am Soc Echocardiogr* 1989; **2(5):**358-67.
7. Veen G, Meyer A, Verheugt FW *et al*. Culprit lesion morphology and stenosis severity in the prediction of reocclusion after coronary thrombolysis: **angiographic results of the APRICOT study. Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis.** *J Am Coll Cardiol* 1993; **22(7):**1755-62.
8. Damman P, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ. **5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial a randomized comparison of an early invasive versus selective invasive management in patients with non-ST-segment elevation acute coronary syndrome.** *J Am Coll Cardiol* 2010; **55(9):**858-64.

9. Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E, Wallentin L. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 2006; **368(9540):**998-1004.
10. Wald DS, Morris JK, Wald NJ *et al*. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med* 2013; **369(12):** 1115-23.
11. Goldstein JA, Demetriou D, Grines CL, Pica M, Shoukfeh M, O'Neill WW. Multiple complex coronary plaques in patients with acute myocardial infarction. *N Engl J Med* 2000; **343(13):**915-22.
12. Windecker S, Kolh P, Alfonso F *et al*. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35(37):**2541-619.
13. Thygesen K, Alpert JS, Jaffe AS *et al*. Third universal definition of myocardial infarction. *Eur Heart J* 2012; **33(20):**2551-67.
14. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000; **36(3):**959-69.
15. Ryan TJ, Antman EM, Brooks NH *et al*. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol* 1999; **34(3):**890-911.
16. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. *Lancet* 1995; **345(8951):**669-85.
17. Pfeffer MA, McMurray JJ, Velazquez EJ *et al*. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; **349(20):**1893-906.
18. Sabatine MS, Cannon CP, Gibson CM *et al*. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; **352(12):**1179-89.